Hyperphosphatemia in Celiac Disease: Hereditary or Acquired Pseudohypoparathyroidism

Çölyak Hastalığında Hiperfosfatemi: Herediter veya Kazanılmış Psödohipoparatiroidizm

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Abstract

Calcium and vitamin D deficiencies caused by intestinal malabsorption in celiac disease lead to severe impairments of calcium and bone metabolisms. Indeed, malabsorption of calcium results in secondary hyperparathyroidism. However, celiac disease may be rarely accompanied by other endocrinopathies such as hypoparathyroidism and primary hyperparathyroidism. We will report a case of celiac disease presenting with hypocalcemic tetany and having hyperparathyroidism accompanied by hyperphosphatemia, suggesting pseudohypoparathyroidism and we will discuss possible diagnoses of the case. *Turk Jem 2007; 11: 127-8*

Key words: Celiac disease, hypocalcemia, hyperphosphatemia, pseudohypoparathyroidism, vitamin D deficiency

Özet

Çölyak hastalığında malabsorbsiyon sonucu gelişen kalsiyum ve vitamin D eksikliği, kalsiyum ve kemik metabolizmasında ağır bozukluklara yol açar. Kalsiyum malabsorbsiyonu, sekonder hiperparatiroidizime neden olur. Bununla birlikte, Çölyak hastalığının, hipoparatiroidizim ve primer hiperparatiroidizim gibi diğer endokrinopatiler ile birlikteliği nadiridr. Bu makalede hipokalsemik tetani ile ortaya çıkan ve labaratuvar bulguları psödohipoparatiroidizmi düşündüren, Çölyak hastalığı olan kadın hastanın olası tanıları tartışılmıştır. *Turk Jem 2007; 11: 127-8*

Anahtar kelimeler: Çölyak hastalığı, hipokalsemi, hiperfosfatemi, psödohipoparatiroidi, vitamin D eksikliği

Introduction

Celiac disease is an autoimmune disease which appears in the form of malabsorption due to gluten intolerance in genetically susceptible people. This disease is usually diagnosed at the age of 2 years and the peaks at the age of 40s (1). Including asymptomatic cases, the prevalence of the disease has been shown to be over 1% in the studies in Western societies using highly sensitive tests such as anti-endomisium antibody and tissue transglutaminase antibody tests (2). Although the clinical picture varies with the extent and severity of intestinal involvement, the disease frequently causes bone and muscle pains, cramps, tetany, rickets and osteoporosis (3).

Here we present a case of celiac disease presenting with hypocalcemic tetany and with laboratory results suggesting pseudohypoparathyroidism (PHP).

Case Report

A 42-year-old woman presented with numbness of the hands and feet to our emergency department. On admission, she had low serum total calcium levels and high phosphorus levels. Therefore, she was administered intravenous calcium gluconate. In her history, it was learnt that the patient had the same complaints during pregnancy. Then, she was found to have hypocalcemia and initiated oral calcium. Although she has been on treatment with oral calcium, she had muscle cramps and tetany and therefore, she was infused calcium occasionally. In the past two months, she had diarrhea which began just after meals and which occurred more than six or seven times in one day and she had a weight loss of 26 kg. The patient underwent thrombectomia for the treatment of thrombosis in the jugular vein 8 years ago and since then she was receiving warfarin 5mg/day for 8 years and oral calcium gluconate for one and a half years. Her sister died of breast carcinoma and her brother and father died of cerebral tumor.

Physical examination revealed that the patient had blood pressure of 90/65 mmHg, heart rate of 113/min and BMI 15 kg/m^2. The skin and conjunctivas were pale. Chovestek and Trousseau signs were positive. Other findings of physical examination were normal.

Laboratory investigations showed normal serum albumin levels, but low levels of total calcium (6,85mg/dL) and high levels of phos-

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phorus (5,5 mg/dL) and intact PTH (107,5 pg/ml). Serum creatinine 0,41mg/dl and serum urea 13mg/dl. Her 24 hours urine sample showed phosphorus 37.25 mg/dl, calcium 6.65 mg/dl, creatinine 38,76 mg/dl and urine volume 1400ml. Creatinine clearance was calculated 91.9 ml/min and fractional tubular resorption of phosphate (TRP) was calculated 92.83. Serum 25(OH)D (29 μg/L) and magnesium (2.43 mg/dl) levels were normal. She had pancytopenia and her blood film demonstrated macrocytosis and neutrophil hypersegmentation. She had low levels of vitamin B12 and folic acid and normal ferritin levels. The patient also had hypokalemia and her aspartate transaminase (AST) level was high. In view of history and laboratory results, the patient was suspected of having celiac disease. She had high levels of anti-tissue transglutaminase (anti-t TG) (105,1 U/Ml) and her duodenal biopsy demonstrated villous flattening, crypt hyperplasia and increased intraepithelial lymphocytes. Duodenal biopsy findings were suggesting celiac disease. Microscopic examination of the feces showed no abnormality. Her protrombine time was 14.4 seonds, activated partial tromboplastine time was 27.2 seconds and PT INR was 1.2. Bone densitometry showed an L2-L4 T score of -3,00, a Z score of -2,6, a femur neck T score of -1,87 and a femur neck Z score of -1,4. The patient was given calcium carbonate, calcitriol, vitamin B12, folic acid and a gluten free diet. Laboratory parameters before and after treatment are shown in the Table below.

Discussion

Severe hypocalcemia and hyperparathyroidism accompanied by hyperphosphotemia is unusual in celiac disease. At first sight, the patient seemed to have celiac disease accompanied by pseudohypoparathyroidism (PHP). PHP is a heterogeneous group of hereditary disease characterized by hypocalcemia, hyperphosphotemia and increased parathormone levels (4). However, the likelihood of acquired PHP should not be overlooked in the case presented here. Hypophoshatemia is the cardinal feature of vitamin D deficiency but hyperphosphatemia is distinctly unusual. In fact, the clinical picture and biochemical features of stage I vitamin D deficiency are very similar to those of type II PHP and stage I vitamin D deficiency can be mistaken for type II PHP (5). Vitamin D deficiencies mimicking type II PHP have been reported to appear especially in childhood (5,6). In the case presented here, presence of high serum phosphate on admission can be explained by resistance of renal tubular cells to PTH which is seen in early stages of vitamin D deficiencies. Treatment with vitamin D and calcium help to improve resistance of renal tubular cells to PTH (7). In fact, there was a case of acquired PHP due to celiac disease in which laboratory results and clinical signs improved after a gluten free diet (8).

More than one factor (local or systemic) plays a role in etiology of hypocalcemia in Celiac disease. Calcium absorption is impaired due to intestinal malabsorption caused by mucosal lesions, which results in subnormal serum calcium levels. Besides, such factors as decreased intake of calcium due to lactose intolerance, precipitation of endogenous calcium in the intestinal lumen due to fat or its decreased reabsoprtion and vitamin D deficiency may also play a role in hypocalcemia. The major stimulus to secondary hyperparathyroidism in celiac disease is calcium deficiency caused by fecal loss of endogenous calcium (9). Furthermore, Selby et al. showed that patients with gluten enteropathy who follow an appropriate diet may develop secondary hyperparathyroidism although they have normal calcium and 25 (OH)D levels (9). This can be attributed to persistence of up-regulated parathyroid activity despite improvement of calcium malabsorption in celiac patients (3).

A case of isolated hypocalcemia due to primary intestinal malabsorption of calcium without vitamin D deficiency because of involvement of the small intestine in the early stages of the celiac disease was reported (10). Similarly, the case presented here had hypocalcemia despite normal serum vitamin D levels. Such cases may lack proteins regulated by vitamin D such as calbindin and calcium-binding protein, which uptake calcium from the intestinal lumen, although vitamin D levels are normal and vitamin D receptors are present in the mucosa (11,12). Warfarin, given for the treatment of thrombosis of the jugular vein, does not have any effects on serum calcium and vitamin D levels.

Unfortunately, we could not confirm the diagnosis of PHP since Ellsworth-Howard test is not performed in our clinic. Our patients had neither any other causes of hyperphosphatemia like renal failure, tumoral calcinosis, heparin or bisphonate therapy nor magnesium depletion. Restoration of phosphaturic response after calcium and vitamin D supplementation in our case suggests that patients presenting with the above mentioned clinical and laboratory signs may have celiac disease accompanied by PHP or secondary hyperparathyroidism due to isolated hypocalcemia and a transient parathyroid hormone resistance and that these conditions should be taken into account in the differential diagnosis.

Table 1. Laboratory parameters before and after treatment

	Before Treatment	After Treatment
Ca	6.85 mg/dl	9.16 mg/dl
P	5.5 mg/dl	4.03 mg/dl
PTH	107.5 pg/dl	48pg/dl
25(OH)D	29 μg/L	60μg/L
Ürea	13 mg/dl	10.9 mg/dl
Creatinine	0.41 mg/dl	0.51 mg/dl
Creatinine Clearance	91.9 ml/sec	112.8 ml/sec
ALP	114 U/L	87 U/L
WBC	3204	5170
HB	9.2g/dl	14.1 g/dl
PLT	62400	236000
MCV	100.8 fl	82.52 fl
Vitamin B12	125 pg/ml	1102 pg/ml
Folic Acid	1.82 ng/ml	14.13 ng/ml
TRP	92.8	88.3
TmP/GFR	5.1 mg/dl	3.3 mg/dl
24 hour urine phosphor	521.5 mg/day	708 mg/day

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